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# The Protective Effects of Pre-Treatment with Glutamate Metabotropic Receptor Agonists on the Development of Parkinsonian Movements

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## 1. Introduction

The subcortical nuclei of the basal ganglia are of great importance in initiation of normal body motor activities. Degeneration of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta has been shown to be the main cause of Parkinson's disease (PD) (Phillips & Brown, 1999; Phillips et al., 2006; and Truong et al., 2006).

Degeneration of dopaminergic neurons within the nigrostriatal pathway following treatment with the neurotoxin 6-hydroxy dopamine (6-OHDA) has been accepted widely as a good model of PD (Wichmann et al., 2002; Willis & Kennedy, 2004; Vernon et al., 2005; Truong et al., 2006; Chaturvedi et al., 2006; Phillips et al., 2006).

Excitatory amino acids play an important role, not only in epilepsy (Coutinhio-Netto et al., 1981; Bradford 1995; Abdul-Ghani et al 1997) but also in some neurodegenerative diseases (Wilkins & Acosta 1995). Excitation of sub-thalamic nucleus neurons in vitro was achieved by activation of group I metabotropic glutamate receptors by (S,R)-dihydroxy-phenylglycine (DHPG), and was blocked by the receptor antagonist (+)-alpha-methyl-4-carboxyphenylglycine (MCPG). No effects were obtained with the selective agonists of group II and group III metabotropic receptors such as L-2-amino-4-phosphonobutyrate (LAP4) and (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl) glycine (DCG-IV) (Abbott et al., 1997). Intra-sub-thalamic injection of (1S,3S)-1-aminocyclopentane-1,3-dicarboxylic acid (1S,3R)-ACPD produced marked contra-lateral rotation, similar to that seen after intra-striatal injection of (1S,3S)-ACPD, suggesting that metabotropic glutamate receptors as a possible target for the treatment of Parkinson's disease (Sacaan et al., 1991: 1992; Kaatz & Albin, 1995). Further more Group-III mGlu receptors stimulation by LAP4 was found to improve akinesia in a rat model of Parkinson's disease (Cuomo et al., 2009). Recently attention has focused on seeking alternative non-dopaminergic strategies in the treatment of basal ganglia disorders, and is now shifting to glutamatergic pathways.

In the current experiments we have tested the effect of pre-treatment with a glutamate metabotropic receptor agonist Sub-type III, LAP4 and a glutamate metabotropic receptor antagonist, MPPG, injected into the median forebrain bundle or to the striatum, on rats

made Parkinsonian by intra-cerebral microinjection of 6-OHDA, as described by Willis and Kennedy (2004).

## 2. Materials and methods

### 2.1 Drugs and chemicals

All chemicals and drugs were of analytical grade and were purchased from Sigma Chemicals Co., USA.

### 2.2 Animals and surgery

Sprague-Dawley rats weighing 180 to 250g were used in all experiments. Rats were kept under environmentally controlled conditions (ambient temperature 22 - 23°C; Humidity 40-50% on a 12 hour light dark cycle with food and water available to ad libitum. Experiments were performed following the guidelines of animal care of the national institute of health, and experiments were approved by the ethical committee in our faculty of medicine. The animals were anaesthetized by intra-peritoneal injection of sodium pentobarbital, 60mg/kg. They were kept under light anaesthesia characterized by a negative response to pain and a positive corneal reflex and the level of anaesthesia was periodically verified via the hind limb compression reflex. Rats were placed on a stereotaxic apparatus; the scalp was then incised to expose the parietal bone. After drilling through the bone, a stainless steel cannula was implanted into the median forebrain bundle, using the following coordinates from the bregma: AP= -1.8 mm, L=  $\pm$  1.8 mm and V = - 6.1 mm, as described by Willis and Armstrong (1999) (The size of the lesion was not confirmed) for the injection of 6-OHDA (16  $\mu$ g in 2  $\mu$ L BPS), and pre-treatment with LAP4 or MPPG. In other experiments a second cannula was implanted in the striatum, coordinates: AP= 1.3 mm, L=  $\pm$  2.4 mm and V = - 7.8 mm, for the injection of LAP4 (40ng / 2 $\mu$ L BP) or MPPG (40ng / 2 $\mu$ L BPS). The volume of 2  $\mu$ L buffer phosphate solution or the same volume of the drugs solution, were slowly micro-injected in a speed of 2  $\mu$ L per 2 min. to avoid brain damage.

Animals were rendered Parkinsonian by the intra-cerebral microinjection of 6-hydroxydopamine (6-OHDA; 16  $\mu$ g in 2  $\mu$ L BPS) into the above coordinates at a flow rate of 1  $\mu$ L/min. LAP4, a selective agonist, or MPPG, a selective antagonist of glutamate metabotropic receptors sub-type III, were unilaterally microinjected into the median forebrain bundle or to the striatum at the same rate of flow, for 15 min before treatment with 6-OHDA.

### 2.3 Measurement of motor activities

Rats were left to move freely over a 20 meters long and 15 meters wide floor with a 20  $\times$  20 centimetre squared grid. Locomotion (spontaneous movement) was measured daily by counting the number of squares crossed and calculating the speed of movement in centimetres per second. The number of rearing and rotation episodes were measured daily by counting the events over 10 minutes. Averages were then calculated per minute. Body weight was measured weekly as an index of eating behaviour and as the percentage change per month was calculated.

### 2.4 Statistics

Values were expressed as mean  $\pm$  standard error of the mean (SEM) for the number of experiments indicated in parentheses. Results were compared, where appropriate, using a

One Way ANOVA with Dunnets post hoc test against 6-OHDA treated animals. Differences were considered statistically significant if  $P < 0.05$ . Statistical analyses were performed using Graph Pad Prism v 3.03.

3. Results

3.1 Induction of Parkinsonism by 6-OHDA

After microinjection of rats with 6-OHDA into the median forebrain bundle, there was a reduction in locomotion speed from  $15.15 \pm 0.61$  (13) to  $8.22 \pm 1.03$  (36) cm/sec. ( $P \leq 0.005$ ) after one week, and progressively reduced to  $3.78 \pm 0.54$  (36) after 4 weeks. Rotation movements were elevated significantly to  $2.64 \pm 0.29$  (36) times per min. after one week and to  $3.58 \pm 0.26$  (24) after 4 weeks. Rearing was increased to  $2.25 \pm 0.33$  (36) and to  $4.75 \pm 0.41$  (24) times per min. after one week and 4 weeks respectively. The normal increase in body weight was reduced from 38% to 2%. (Fig. 1 and Table 1). 6-OHDA progressively reduced spontaneous movements which became minimal after 4 to 5 weeks (Fig. 2).

		Rotation (No/min)	Rearing (No/min)	% change Body Weight
Sham Control (2μL BPS)		$0.31 \pm 0.24$ (13)	$0.15 \pm 0.10$ (13)	↑38%
6-OHDA (16μg/2μL)	1 <sup>st</sup> Week	$2.64 \pm 0.29$ (36) +	$2.25 \pm 0.33$ (36)**	
	4 <sup>th</sup> Week	$3.58 \pm 0.26$ (24)**	$4.75 \pm 0.41$ (24)**	↑2%
LAP4 (40ng/2μL) + 6-OHDA (16μg/2μL)	1 <sup>st</sup> Week	$1.47 \pm 0.26$ (47)* ↓35%	$0.39 \pm 0.11$ (48)*** ↓83%	
	4 <sup>th</sup> Week	$1.41 \pm 0.17$ (44)*** ↓61%	$0.35 \pm 0.12$ (45)*** ↓93%	↑37%
MPPG (40ng/2μL) + 6-OHDA (16μg/2μL)	1 <sup>st</sup> Week	$1.84 \pm 0.33$ (31)	$1.90 \pm 0.35$ (31)	
	4 <sup>th</sup> Week	$1.57 \pm 0.19$ (49)** ↓56%	$3.90 \pm 0.43$ (38)	↑22%

Table 1. Effect of pre-treatment with LAP4 and MPPG on motor disorders induced by 6-OH-Dopamine

LAP4 or MPPG (40 ng/2μL) were injected intra-cerebrally into the same site in the median forebrain bundle (Coordinates (AP= -1.8; L=1.8; V= -6.1) 15 min. before injection of 6-OHDA (16 μg / 2μL BPS). Sham control was injected for the same period with the same volume of BPS. Percentage change in body weight and other motor disorders were recorded during the first and the fourth weeks of treatment.

Values are Mean ± SEM and the number of experiments is indicated between brackets.

+  $P \leq 0.001$ ;      ++  $P \leq 0.0005$       Compared to Sham control animals  
\*  $P \leq 0.05$ ;      \*\*  $P \leq 0.002$ ;      \*\*\*  $P \leq 0.0005$       Compared to 6-OHDA treated animals

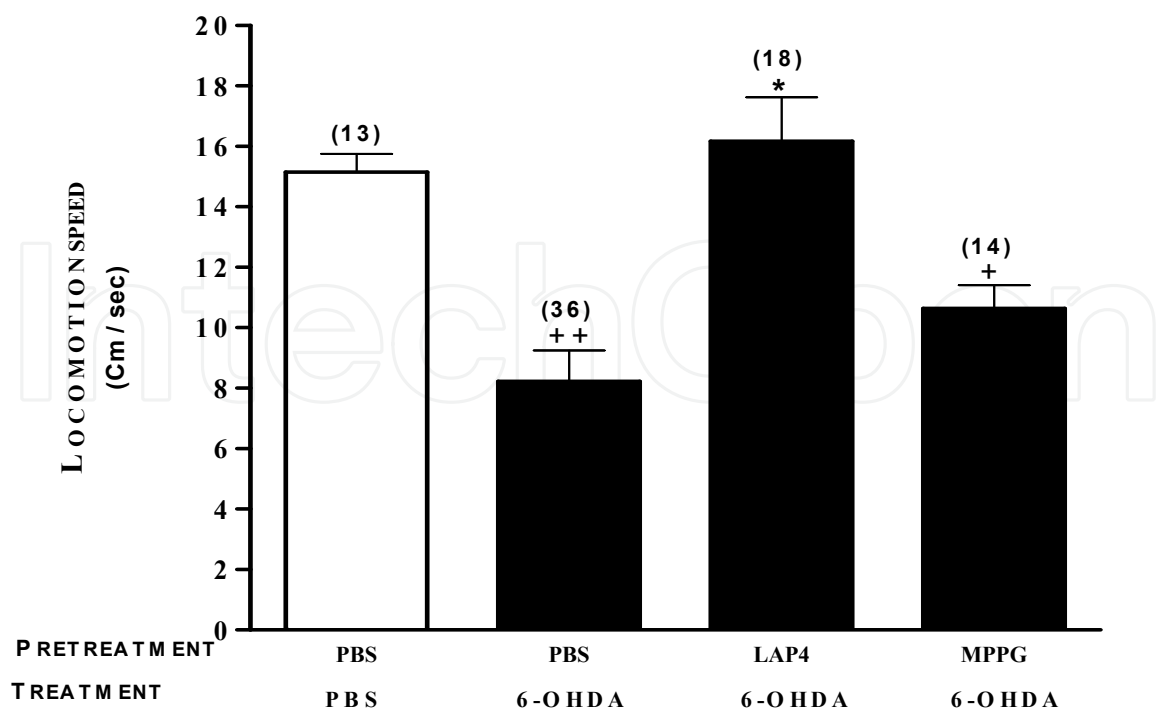


Fig. 1. Effect of pre-treatment with LAP4 and MPPG on Locomotion Disorders induced by injection of 6-OH-Dopamine

LAP4 or MPPG (40 ng / 2μL BPS) were injected intra-cerebrally into the same site in the median forebrain bundle coordinates (Coordinates: AP=-1.8; L=1.8; V=-6.1) 15 min. before injection of 6-OHDA (16 μg / 2μl BPS). Sham control animals were injected for the same period with the same volume of BPS. Locomotion measurements were recorded after one week of treatment.

Values are mean ± SEM for the number of experiments indicated in brackets.

- \* P ≤ 0.005                Compared to 6-OHDA treated animals
- + P ≤ 0.01                Compared to sham control animals
- ++ P ≤ 0.005            Compared to sham control animals

3.2 Pre-treatment with LAP4

Pre-treatment with LAP4 before injection of 6-OHDA increased locomotion by 97 % after one week, from 8.22 ± 1.03 (36) to 16.17 ± 1.46 (18) (P ≤ 0.005), and by 146% after 4 weeks, from 3.78 ± 0.54 (36) to 9.29 ± 1.28 (14) (P ≤ 0.01) (Figs 1 and Table 2). Rotation was reduced significantly by 57% from 3.58 ± 0.26 (24) to 1.55 ± 0.26 (18) (P ≤ 0.0005) after 4 weeks. Rearing was reduced by 85% from 2.25 ± 0.33 (36) to 0.33 ± 0.21(12) after one week, and with the same percentage after 4 weeks, from 4.75 ± 0.41 (24) to 0.73 ± 0.07 (15) (P ≤ 0.0005). LAP4 prevented the effect of 6-OHDA on body weight, percentage change in body weight was increase from 2% to 38 % (Table 1). The protective effect of LAP4 was consistent for one to 5 weeks after injection of 6-OH Dopamine. (Fig.2)

LAP4 or MPPG (40 ng/2μL) were injected intra-cerebrally into the median forebrain bundle coordinates (AP= -1.8; L=1.8; V= -6.1) 15 min. before injection of 6-OHDA (16 μg / 2μL BPS) into the same site. Sham control values of locomotion 15.15 ± 1.61 (13) cm/sec at 0 time and after 5 weeks 14.38 ± 1.25 (13) cm/sec. Values are Mean ± SEM.

\* P ≤ 0.05; \*\* P ≤ 0.01; \*\*\* P ≤ 0.005    compared to animals treated with 6-OHDA alone.

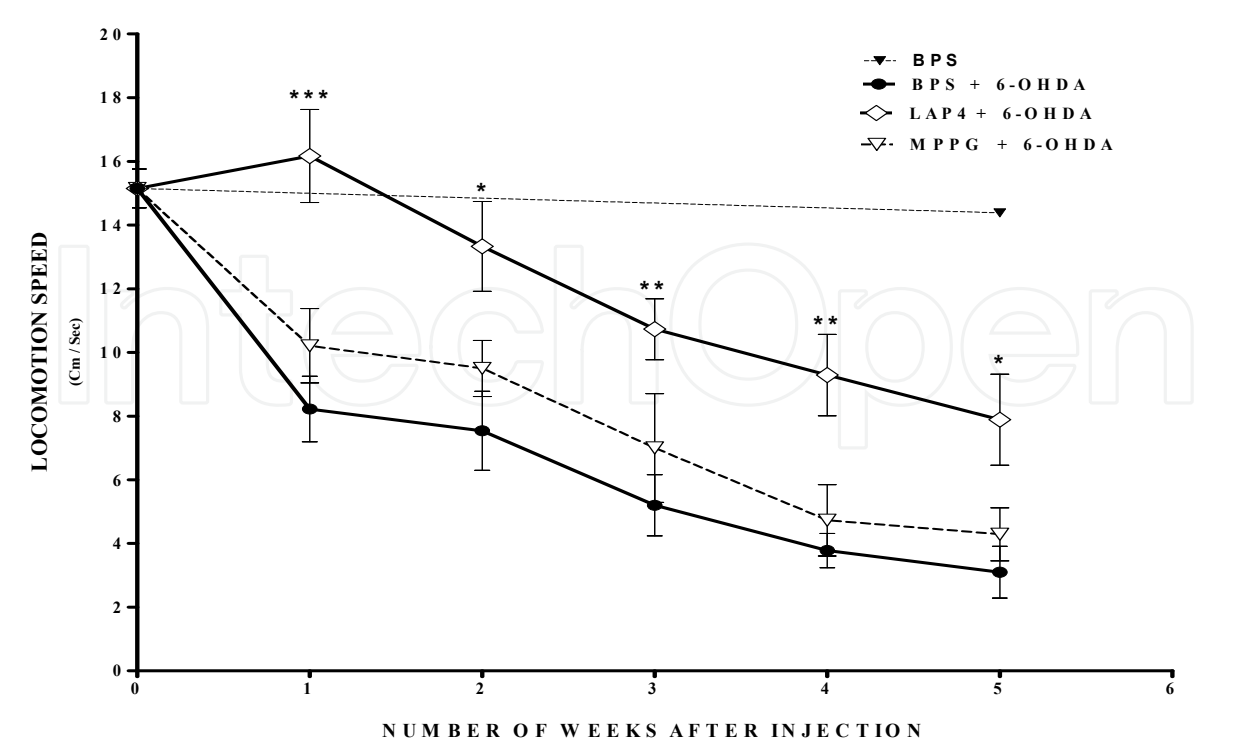


Fig. 2. Effect of pre-treatment with LAP4 and MPPG in Locomotion Disorders induced by 6-OHDA

3.3 Pre-treatment with MPPG

Injection of the glutamate metabotropic antagonist, MPPG, into the striatum instead of LAP4 15 min. before injection of 6-OHDA had no significant effect on motor disorders induced by 6-OHDA (Fig. 1 and Tables 1). However, the effect of 6-OHDA on body weight was largely reversed, from 2% to 22%, and rearing was reduced by 56% after one month of treatment (Table 1).

3.4 Comparison between Injection of LAP4 into the Median Forebrain Bundle (MFB) and Striatum

When LAP4 was intra-cerebrally micro-injected into MFB or Striatum 15 min. prior to the injection of 6-OHDA, it produced significant increase in locomotion one week after the injection (97% increase and 82% increase respectively). The increase was even more after one month (146% and 138% respectively).

There was a small decrease in rotational movement after one week of injection (9% decrease when LAP4 was injected into MFB and 36% decrease when LAP4 was injected into Striatum). The decrease was even higher one month later (57% and 63% respectively).

Similar results were obtained when rearing movement was calculated. A significant decrease was produced one week after LAP4 injection into MFB or striatum (85% and 81% respectively). The decrease persists after one month (85% and 87% respectively).

These results showed no significant difference in the protective effect of LAP4 on motor disorders produced by the injection of 6-OHDA according to its site of injection.

LAP4 or MPPG (40 ng/2μL) were injected intra-cerebrally into the median forebrain bundle (NSB) coordinates (AP= -1.8; L=1.8; V= -6.1) or into the striatum coordinates (AP= 1.3;



L=±2.4; V= -7.8) 15 min. before injection of 6-OHDA (16 µg / 2µL BPS) into the median forebrain bundle. Sham control was injected for the same period with the same volume of BPS. Percentage change in body weight and other motor disorders were recorded during the first and the fourth weeks of treatment.

		Without LAP4		With LAP4	
		Sham Control	6-OHDA	MFB V= - 6.1	Striatum V= - 7.8
Locomotion (cm/sec.)	1 <sup>st</sup> Week	15.15 ± 0.61 (13)	8.22 ± 1.03 (36)	16.17 ± 1.46 (18)** ↑97%	14.96 ± 0.99 (26)** ↑82%
	4 <sup>th</sup> Week		3.78 ± 0.54 (36)	9.29 ± 1.28 (14)* ↑146%	9.00 ± 1.13 (18)** ↑138%
Rotation (times/min.)	1 <sup>st</sup> Week	0.31 ± 0.24 (13)	2.64 ± 0.29 (36)	2.39 ± 0.46 (18)	1.69 ± 0.33 (36)
	4 <sup>th</sup> Week		3.58 ± 0.26 (24)	1.55 ± 0.26 (18)*** ↓57%	1.31± 0.23 (26) **** ↓63%
Rearing (times/min.)	1 <sup>st</sup> Week	0.15 ± 1.0 (13)	2.25 ± 0.33 (36)	0.33 ± 0.21 (12)** ↓85%	0.42 ± 0.13 (36)*** ↓81%
	4 <sup>th</sup> Week		4.75 ± 0.41 (24)	0.73 ± 0.07 (15)**** ↓85%	0.63 ± 0.22 (35)**** ↓87%

Table 2. Differences between the intra-cerebral injection of LAP4 into the Median Forebrain Bundle (MFB) or the striatum

Percentage change in LAP4 pre-treated animals are compared to animals treated with 6-OHDA without pre-treatment with LAP4.  
Values are Mean ± SEM and the number of experiments is indicated between brackets.  
\* P ≤ 0.01; \*\* P ≤ 0.005; \*\*\* P ≤ 0.001; \*\*\*\* P ≤ 0.0005 compared to 6-OHDA treated animals

4. Discussion

Our results show that nigrostriatal micro-injection of 6-OHDA reduced significantly spontaneous locomotion in rats by 46% after one week and 75% after 4 weeks, and reduced the normal gain in body weight by 95%, which indicates a reduction in feeding. Rearing and rotation movements increased by 15 and 9-fold respectively after one week, and by 32 and 12-fold respectively after four weeks. Other workers have made rats Parkinsonian by micro-injection of 6-OHDA into the striatum (Kirik et al., 1989; Chaturvedi et al., 2006), the nigrostriatal bundle (Willis & Kennedy, 2004) or the substantia nigra pars compacta (Vernon et al., 2005). Lopez et al. (2007) found that LAP4 infusion into the globus pallidus reduced abnormal activities associated with Parkinsonism, as did our infusion into the nigrostriatal bundle.

LAP4, a selective agonist of group III metabotropic receptors, had a protective effect against the development of motor disorders induced by 6-OHDA when it was micro-injected into the median forebrain bundle. It increased locomotion significantly and reduced motor disorders induced by 6-OHDA by an average of 39% during the first month. It also prevented the effect of 6-OHDA on body weight. In addition LAP4 has reduced significantly motor disorders like rotations and rearing by 61% and 93% respectively. The neuroprotective effect of LAP4 was reported in vitro against rotenone which causes Parkinsonian features in rats (Jiang et al., 2006) and in vivo against 6-OHDA toxicity (Lafon-Cazal et al., 1999; Bruno et al., 2000; Vernon et al., 2005; 2007). The potent and systemically active group II mGlu2/3 receptor agonist (-)-2-oxa-4-aminocyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268), was found to provided some protection against nigral and striatal infusion of 6-OHDA (Murray et al., 2002).

We found that in-vivo intra-nigrostriatal injection of glutamate metabotropic antagonist (MPPG) before injection of 6-OHDA had no significant effect on locomotion, rotation movement or rearing, but had a significant effect on body weight changes. Therefore, whereas the development of locomotion disorders induced by injection of 6-OHDA was reduced by pre-treatment with LAP4, a glutamate presynaptic agonist, it was not affected by the selective antagonist, MPPG. Glutamate metabotropic antagonists are known to increase calcium ion uptake in presynaptic membranes (Abdul-Ghani et al., 1997) and increase glutamate release from presynaptic membranes. This could explain the lack of effect of the antagonist on locomotion which we have observed. Similar protective activity was achieved when LAP4 was injected at the same volume and concentration to the striatum coordinates: (AP= 1.3 mm, L=  $\pm$  2.4 mm and V = - 7.8). Significant histological and functional protection of the nigrostriatal tract against 6-OHDA toxicity by LAP4 was reported by Vernon et al 2005.

Excessive release of glutamate by neurons feeding into the striatum and substantia nigra could stimulate NO production and iron release, causing an increase in free radicals and oxidative damage to neurons (Snyder & Brecht, 1992; Youdim et al., 1993; Gerlach et al., 1994; Hugon et al., 1996). Perhaps, therefore, agents which inhibit glutamate release in the substantia nigra and striatum may be expected to protect neurons in patients with Parkinson's disease. Vernon et al. (2006) have shown that acute or sub-chronic intra-nigral injection of LAP4 provides significant protection of the nigrostriatal system against 6-OHDA toxicity, and this effect was blocked when LAP4 was co-administered with the selective group III metabotropic glutamate receptor antagonist (R,S)-alpha-methylserine-O-phosphate (MSOP), confirming a receptor-mediated mechanism of action. Whether the neuroprotective effect is due to reduction in glutamate release or due to possible glial cell-related mechanism which may involve increased glutamate uptake by astrocytes (Yao et al., 2005), or production of neurotrophic factors which limit nigrostriatal damage as reported by (Bruno et al., 1997, 1998; Ciccurelli et al., 1999; Matarredona et al., 2001).

It is known that LAP4 is a glutamate presynaptic agonist, with selective activity against group III receptors, and that it inhibits  $\text{Ca}^{++}$  uptake into presynaptic membranes and inhibits the release of glutamate and aspartate (Vazquez et al., 1995; Abdul-Ghani et al., 1997; Han et al., 2004 and Vernon et al., 2005), likely by negatively modulating voltage-dependent  $\text{Ca}^{++}$  channels and  $\text{Ca}^{++}$ -dependent neurotransmitter release (Conn & Pin 1997). These actions explain its anti-epileptogenic and anti-seizure activity, as reported by Abdul-Ghani et al., (1997), and its anti-Parkinsonian activity shown in the present paper. As long ago as 1996, Nicoletti et al suggested that pharmacological agents which reduce glutamate transmission



in the basal ganglia might have a neuroprotective effect in patients with Parkinson's disease. The results we report here show that LAP4 is one such agent whose potential in controlling Parkinsonian features warrants further exploration.

## 5. Conclusion

Our results show that the glutamate metabotropic agonist LAP4 opposes the development of Parkinsonian features induced in rats by infusing 6-OHDA into the corpus striatum. Such agents may offer a non-dopaminergic method of treating Parkinson's disease.

## 6. Acknowledgement

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## **Towards New Therapies for Parkinson's Disease**

Edited by Prof. David Finkelstein

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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of  $\alpha$ -synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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